

CLAIMS

SVb
A1
5

1. A composition comprising:
- (a) a drug in a pharmaceutically acceptable solubility-improved form; and
- (b) a concentration-enhancing polymer combined with said solubility-improved form in a sufficient amount so that said composition provides, after introduction to a use environment, a maximum concentration of said drug in said use environment that is at least 1.25-fold an equilibrium concentration of said drug in said use environment, and a concentration of said drug in said use environment that exceeds said equilibrium concentration for a longer time than the concentration of said drug in said use environment provided by a control composition exceeds said equilibrium concentration, wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form.

2. The composition of claim 1 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

3. The composition of claim 1 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

4. The composition of claim 1 wherein said drug in said solubility-improved form is amorphous.

09742785 122000

5. The composition of claim 1 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solubilizing agent.

5
6. The composition of claim 5 wherein said solubilizing agent is selected from the group consisting of surfactants, pH control agents, glycerides, partial glycerides, glyceride derivatives, polyoxyethylene and polyoxypropylene ethers and their copolymers, sorbitan esters, polyoxyethylene sorbitan esters, alkyl sulfonates, and cyclodextrins.

15
7. The composition of claim 6 wherein said pH control agents are selected from the group consisting of buffers, organic acids, organic acid salts, organic and inorganic bases, and organic and inorganic base salts.

20
8. The composition of claim 5 wherein said drug is basic and said solubilizer is an organic acid selected from the group consisting of adipic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid, erythorbic acid, maleic acid, L-aspartic acid, L-glutamic acid, tannic acid, and D,L-tyrosine.

30
9. The composition of claim 1 wherein said drug in said solubility-improved form is a solution of a drug substantially dissolved in a liquid to a concentration that is at least 10-fold said equilibrium concentration of said drug in said use environment.

35
10. The composition of claim 9 wherein said liquid is selected from the group consisting of water-immiscible triglyceride vegetable oils, water-immiscible refined and synthetic and semisynthetic oils, mono-, di-

000221-582460

and tri-glycerides, water-miscible alcohols, and water-miscible polyethyleneglycols.

11. The composition of claim 9 wherein said
5 liquid comprises water and a water-soluble solubilizer.

12. The composition of claim 1 wherein said
use environment is *in vivo*.

10 13. The composition of claim 12 wherein said
use environment is selected from the group consisting of
the GI tract, subcutaneous space, vaginal tract,
pulmonary tract, arterial and venous blood vessels, and
intramuscular tissue of an animal.

15 14. The composition of claim 1 wherein said
use environment is *in vitro*.

20 15. The composition of claim 1 wherein said
concentration-enhancing polymer has a hydrophobic portion
and a hydrophilic portion.

25 16. The composition of claim 1 wherein said
concentration-enhancing polymer is a cellulosic ionizable
polymer that is soluble in said use environment when
ionized.

30 17. The composition of claim 16 wherein said
polymer is selected from the group consisting of
cellulose acetate phthalate, methyl cellulose acetate
phthalate, ethyl cellulose acetate phthalate,
hydroxypropyl cellulose acetate phthalate, hydroxypropyl
methyl cellulose acetate phthalate, hydroxypropyl
cellulose acetate phthalate succinate, cellulose
35 propionate phthalate, hydroxypropyl cellulose butyrate
phthalate, cellulose acetate trimellitate, methyl
cellulose acetate trimellitate, ethyl cellulose acetate

00022T" 582460

5
10

15
20

20

25
30

30

35

5 23. The composition of claim 1 wherein said
polymer is a non-ionizable, non-cellulosic polymer.

25. The composition of claim 1 wherein said composition provides a dissolution area under the concentration versus time curve in a use environment for a period of at least 90 minutes during the 1200 minutes immediately following introduction to said use environment that is at least 1.25-fold the corresponding area under the curve provided by said control composition.

27. The composition of claim 1 wherein said composition provides a relative bioavailability of at least 1.25.

35 28. The composition of claim 1 wherein said
composition provides a maximum concentration in said use
environment that is at least 1.25-fold the maximum drug

29. The composition of claim 1 wherein said
5 drug is selected from antihypertensives, antianxiety
agents, anticlotting agents, anticonvulsants, blood
glucose-lowering agents, decongestants, antihistamines,
antitussives, antineoplastics, beta blockers, anti-
inflammatories, antipsychotic agents, cognitive
10 enhancers, cholesterol-reducing agents, antiobesity
agents, autoimmune disorder agents, anti-impotence
agents, antibacterial and antifungal agents, hypnotic
agents, anti-Parkinsonism agents, anti-Alzheimer's
disease agents, antibiotics, anti-depressants, and
15 antiviral agents.

sub
A2

20 (b) a concentration-enhancing polymer
combined with said drug in a sufficient
amount so that said composition provides,
after introduction to a use environment,
a dissolution area under the
25 concentration versus time curve in said
use environment for a period of at least
90 minutes during the 1200 minutes
immediately following introduction to
said use environment that is at least
30 1.25-fold the corresponding area under
the curve provided by a control
composition, wherein said control
composition is free from said
concentration-enhancing polymer and
35 comprises an equivalent quantity of said
drug in said solubility-improved form.

5 32. The composition of claim 30 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

34. The composition of claim 30 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solubilizing agent.

25 36. The composition of claim 35 wherein said
pH control agents are selected from the group consisting
of buffers, organic acids, organic acid salts, organic
and inorganic bases, and organic and inorganic base
salts.

37. The composition of claim 34 wherein said drug is basic and said solubilizer is an organic acid selected from the group consisting of adipic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid, erythorbic acid, maleic acid, L-aspartic acid, L-glutamic acid, tannic acid, and D,L-tyrosine.

38. The composition of claim 30 wherein said drug in said solubility-improved form is a solution of a drug substantially dissolved in a liquid to a concentration that is at least 10-fold said equilibrium concentration of said drug in said use environment.

39. The composition of claim 38 wherein said liquid is selected from the group consisting of water-immiscible triglyceride vegetable oils, water-immiscible refined and synthetic and semisynthetic oils, mono-, di-, and tri-glycerides, water-miscible alcohols, and water-miscible polyethyleneglycols.

40. The composition of claim 38 wherein said liquid comprises water and a water-soluble solubilizer.

41. The composition of claim 30 wherein said use environment is *in vivo*.

42. The composition of claim 41 wherein said use environment is selected from the group consisting of the GI tract, subcutaneous space, vaginal tract, pulmonary tract, arterial and venous blood vessels, and intramuscular tissue of a mammal.

43. The composition of claim 30 wherein said use environment is *in vitro*.

44. The composition of claim 30 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

45. The composition of claim 30 wherein said concentration-enhancing polymer is a cellulosic ionizable polymer that is soluble in said use environment when ionized.

009742785.122000

20

30

30

35

cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose.

50. The composition of claim 30 wherein said
5 polymer is an ionizable, non-cellulosic polymer.

51. The composition of claim 50 wherein said
polymer is selected from the group consisting of
carboxylic acid functionalized polymethacrylates,
10 carboxylic acid functionalized polyacrylates, amine-
functionalized polyacrylates, amine-fuctinoalized
polymethacrylates, proteins, and carboxylic acid
functionalized starches.

52. The composition of claim 30 wherein said
15 polymer is a non-ionizable, non-cellulosic polymer.

53. The composition of claim 52 wherein said
polymer is selected from the group consisting of
20 polyvinyl alcohols that have at least a portion of their
repeat units in the unhydrolyzed (vinyl acetate) form,
polyvinyl alcohol polyvinyl acetate copolymers,
polyethylene glycol, polyethylene glycol polypropylene
glycol copolymers, polyvinyl pyrrolidone, polyethylene
25 polyvinyl alcohol copolymers, and chitin.

54. The composition of claim 30 wherein said
composition provides a maximum concentration of said drug
in said use environment that is at least 1.25-fold said
30 equilibrium concentration of said drug provided by said
control.

55. The composition of claim 30 wherein said
composition provides a relative bioavailability of at
35 least 1.25-fold.

000227-5824260

56. The composition of claim 30 wherein said drug is selected from antihypertensives, antianxiety agents, anticlotting agents, anticonvulsants, blood glucose-lowering agents, decongestants, antihistamines, antitussives, antineoplastics, beta blockers, anti-inflammatory, antipsychotic agents, cognitive enhancers, cholesterol-reducing agents, antiobesity agents, autoimmune disorder agents, anti-impotence agents, antibacterial and antifungal agents, hypnotic agents, anti-Parkinsonism agents, anti-Alzheimer's disease agents, antibiotics, anti-depressants, and antiviral agents.

57. The composition of claim 30 wherein said drug concentration provided by said composition is greater than the equilibrium concentration of said drug for at least 15 minutes.

58. A composition comprising:
 (a) a drug in a pharmaceutically acceptable solubility-improved form; and
 (b) a concentration-enhancing polymer combined with said drug in a sufficient amount so that said composition provides, after introduction to a use environment, a relative bioavailability of at least 1.25.

59. The composition of claim 58 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

60. The composition of claim 58 wherein said drug in said solubility-improved form is a high energy crystalline form of said drug.

61. The composition of claim 58 wherein said drug in said solubility-improved form is amorphous.

0000227 5824260

20

25

35

5

10

15

20

30

35

68. The composition of claim 66 wherein said liquid comprises water and a water-soluble solubilizer.

69. The composition of claim 58 wherein said use environment is *in vivo*.

70. The composition of claim 88 wherein said use environment is selected from the group consisting of the GI tract, subcutaneous space, vaginal tract, pulmonary tract, arterial and venous blood vessels, and intramuscular tissue of an animal.

71. The composition of claim 58 wherein said use environment is *in vitro*.

72. The composition of claim 58 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

73. The composition of claim 58 wherein said concentration-enhancing polymer is a cellulosic ionizable polymer that is soluble in said use environment when ionized.

74. The composition of claim 73 wherein said polymer is selected from the group consisting of cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate

09742785-122000

5

15

20

25

30

35

80. The composition of claim 58 wherein said polymer is a non-ionizable, non-cellulosic polymer.

81. The composition of claim 80 wherein said
5 polymer is selected from the group consisting of
polyvinyl alcohols that have at least a portion of their
repeat units in the unhydrolyzed (vinyl acetate) form,
polyvinyl alcohol polyvinyl acetate copolymers,
polyethylene glycol, polyethylene glycol polypropylene
10 glycol copolymers, polyvinyl pyrrolidone, polyethylene
polyvinyl alcohol copolymers, and chitin.

82. The composition of claim 58 wherein said composition provides a maximum concentration of said drug in said use environment that is at least 1.25-fold said equilibrium concentration of said drug provided by said control.

83. The composition of claim 58 wherein said
20 composition provides a maximum concentration of said drug
in said use environment that is at least 2-fold said
equilibrium concentration.

84. The composition of claim 58 wherein said
25 drug is selected from antihypertensives, antianxiety
agents, anticlotting agents, anticonvulsants, blood
glucose-lowering agents, decongestants, antihistamines,
antitussives, antineoplastics, beta blockers, anti-
inflammatories, antipsychotic agents, cognitive
30 enhancers, cholesterol-reducing agents, antiobesity
agents, autoimmune disorder agents, anti-impotence
agents, antibacterial and antifungal agents, hypnotic
agents, anti-Parkinsonism agents, anti-Alzheimer's
disease agents, antibiotics, anti-depressants, and
35 antiviral agents.

85. The composition of claim 58 wherein said drug concentration provided by said composition exceeds

the equilibrium concentration of said drug for at least 15 minutes.

506
A 4 5 86 A method of administering a drug comprising co-administering to a patient in need of said drug:

- (a) a drug in a solubility-improved form; and
- (b) a concentration-enhancing polymer;

wherein said concentration-enhancing polymer is
10 co-administered with said solubility-improved form in a sufficient amount, so that after introduction to a use environment, a maximum concentration of said drug in said use environment is provided that is at least 1.25-fold an
15 equilibrium concentration of said drug in said use environment provided by a control composition;

and wherein a concentration of said drug in said use environment is provided that exceeds said equilibrium concentration for a longer time than the concentration of said drug in said use environment
20 provided by said control composition exceeds said equilibrium concentration;

and wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-
25 improved form.

87. The method of claim 86 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

30

88. The method of claim 86 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

35

89. The method of claim 86 wherein said drug in said solubility-improved form is amorphous.

09742785 122000

90. The method of claim 86 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solubilizing agent.

5

91. The method of claim 86 wherein said drug in said solubility-improved form is a solution of a drug substantially dissolved in a liquid to a concentration that is at least 10-fold an equilibrium concentration of said drug in said use environment.

10

92. The method of claim 86 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

15

93. The method of claim 86 wherein said concentration-enhancing polymer is a cellulosic ionizable polymer that is soluble in said use environment when ionized.

20

94. The method of claim 93 wherein said polymer is selected from the group consisting of cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose

35

000000 "5822460

5

10

15

20

25

30

35

101. The method of claim 100 wherein said polymer is selected from the group consisting of

5

10

15

20

105. The method of claim 86 wherein said drug is administered in a composition also comprising said concentration-enhancing polymer.

A5 ^{sub} 7
106. A method of administering a drug comprising co-administering to a patient in need of said drug:

- 5 (a) a drug in a solubility-improved form; and
(b) a concentration-enhancing polymer;

wherein said concentration-enhancing polymer is co-administered with said drug in a sufficient amount so that, after introduction to a use environment, a dissolution area under the concentration versus time
10 curve is provided in said use environment for a period of at least 90 minutes during the 1200 minutes immediately following introduction to said use environment that is at least 1.25-fold the corresponding area under the curve provided by a control composition;

15 and wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form.

20 107. The method of claim 106 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

25 108. The method of claim 106 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

30 109. The method of claim 106 wherein said drug in said solubility-improved form is amorphous.

35 110. The method of claim 106 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solubilizing agent.

111. The method of claim 106 wherein said drug in said solubility-improved form is a solution of a drug substantially dissolved in a liquid to a concentration

000027 5824260

112. The method of claim 106 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

114. The method of claim 113 wherein said polymer is selected from the group consisting of cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, hydroxypropyl salicylic acid cellulose acetate, ethylbenzoic acid cellulose acetate, hydroxypropyl ethylbenzoic acid cellulose acetate, ethyl phthalic acid cellulose acetate, ethyl nicotinic acid cellulose acetate, and ethyl picolinic acid cellulose acetate.

115. The method of claim 114 wherein said polymer is selected from the group consisting of

5 116. The method of claim 106 wherein said polymer is a non-ionizable cellulosic polymer.

117. The method of claim 106 wherein said polymer is selected from the group consisting of hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, and hydroxyethyl ethyl cellulose.

15 118. The method of claim 106 wherein said
polymer is an ionizable, non-cellulosic polymer.

119. The method of claim 118 wherein said polymer is selected from the group consisting of
20 carboxylic acid functionalized polymethacrylates,
carboxylic acid functionalized polyacrylates, amine-
functionalized polyacrylates, amine-fuctinoalized
polymethacrylates, proteins, and carboxylic acid
functionalized starches.

120. The method of claim 106 wherein said polymer is a non-ionizable, non-cellulosic polymer.

121. The method of claim 120 wherein said
30 polymer is selected from the group consisting of
polyvinyl alcohols that have at least a portion of their
repeat units in the unhydrolyzed (vinyl acetate) form,
polyvinyl alcohol polyvinyl acetate copolymers,
polyethylene glycol, polyethylene glycol polypropylene
35 glycol copolymers, polyvinyl pyrrolidone, polyethylene
polyvinyl alcohol copolymers, and chitin.

5

10

15

20

25

30

35

128. The method of claim 126 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

130. The method of claim 126 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solubilizing agent.

15 132. The method of claim 126 wherein said
concentration-enhancing polymer has a hydrophobic portion
and a hydrophilic portion.

133. The method of claim 126 wherein said
20 concentration-enhancing polymer is a cellulosic ionizable
polymer that is soluble in said use environment when
ionized.

134. The method of claim 133 wherein said
25 polymer is selected from the group consisting of
cellulose acetate phthalate, methyl cellulose acetate
phthalate, ethyl cellulose acetate phthalate,
hydroxypropyl cellulose acetate phthalate, hydroxypropyl
methyl cellulose acetate phthalate, hydroxypropyl
30 cellulose acetate phthalate succinate, cellulose
propionate phthalate, hydroxypropyl cellulose butyrate
phthalate, cellulose acetate trimellitate, methyl
cellulose acetate trimellitate, ethyl cellulose acetate
trimellitate, hydroxypropyl cellulose acetate
35 trimellitate, hydroxypropyl methyl cellulose acetate
trimellitate, hydroxypropyl cellulose acetate
trimellitate succinate, cellulose propionate
trimellitate, cellulose butyrate trimellitate, cellulose

5

10

15

20

25

30

35

5

10

15

20

25

30

- 35

assemblies having a size of from about 10 to 1000 nanometers; and

- (c) said solution having a maximum concentration of said drug that is at least 1.25-fold an equilibrium concentration of said drug in said use environment, and a concentration of said drug that exceeds said equilibrium concentration for a longer time than the concentration of said drug in said use environment provided by a control composition exceeds said equilibrium concentration, wherein said control composition is free from said concentration-enhancing polymer and comprises an equivalent quantity of said drug in said solubility-improved form.

147. The solution of claim 146 wherein said drug in said solubility-improved form is a crystalline highly soluble salt form of said drug.

148. The solution of claim 146 wherein said drug in said solubility-improved form is a high-energy crystalline form of said drug.

149. The solution of claim 146 wherein said drug in said solubility-improved form is amorphous.

150. The solution of claim 146 wherein said drug in said solubility-improved form is a composition comprising a mixture of said drug and a solid solubilizing agent.

151. The solution of claim 146 wherein said use environment is *in vivo*.

152. The solution of claim 146 wherein said use environment is selected from the group consisting of the GI tract, subcutaneous space, vaginal tract, pulmonary tract, arterial and venous blood vessels, and intramuscular tissue of an animal.

153. The solution of claim 146 wherein said use environment is *in vitro*.

154. The solution of claim 146 wherein said concentration-enhancing polymer has a hydrophobic portion and a hydrophilic portion.

155. An aqueous solution formed by administration of a drug in a solubility-improved form and a concentration-enhancing polymer to a use environment, comprising:

- (a) each of said drug and said concentration-enhancing polymer being at least partially dissolved in said solution;
- (b) at least a portion of said dissolved drug being associated with at least a portion of said polymer in a plurality of assemblies of drug and polymer, said assemblies having a size of from about 10 to 1000 nanometers;
- (c) said polymer being selected from the group consisting of hydroxypropyl methyl cellulose acetate succinate, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, methyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, cellulose acetate trimellitate, cellulose acetate terephthalate and cellulose acetate isophthalate; and
- (d) said solution having a maximum concentration of said drug that is at

least 1.25-fold an equilibrium
concentration of said drug in said use
environment, and a concentration of said
drug that exceeds said equilibrium
concentration for a longer time than the
concentration of said drug in said use
environment provided by a control
composition exceeds said equilibrium
concentration, wherein said control
composition is free from said
concentration-enhancing polymer and
comprises an equivalent quantity of said
drug in said solubility-improved form.

5

10

00022T 582460